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09/155,739	09/11/1998	MARY M. BENDIG	15270-001430	9068

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	09/155739	BENDIG ET AL
	Examiner: GAMBEL	Art Unit: 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 3/11/02

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) 2-16 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 1, 17-26

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on 4/11/98 is/are: a)☐ accepted or b)☑ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☑ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 1 .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. Applicant's amendment, filed 3/11/02 (Paper No. 13), has been entered.
Claims 1-26 have been amended.

2. Applicant's election of the species rheumatoid arthritis in Paper No. 13, filed 3/11/02, is acknowledged.

Claims 1 and 17-26 are under consideration in the instant application.

Claims 2-16 have been withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected species.

3. Applicant's amendment of the first line of the specification to indicate priority is acknowledged.

It is noted that there are differences between the first line of the specification and the oath and declaration. The oath and declaration include USSN 08/186,269 and WO95/01219 which are not indicated on the first line of the specification. Applicant is invited to clarify the appropriate priority documents on the first line of the specification.

The filing date of the instant claims is deemed to be the filing date of the priority application PCT US96/18807, filed 11/21/96, as the earlier priority applications do not provide written support for treating "rheumatoid arthritis" (as well as the other non-elected diseases), and thus does not support the claimed limitations of the instant application.

If applicant desires priority prior to 11/21/96; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

5. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

6. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

7. It is noted that a number of pages in the specifications have faint or missing words.

Applicant may consider providing a substitute specification or may consider discussing the issue with the examiner in order to correct the deficiencies in the specification.

If a substitute specification is submitted to correct the numerous entries to be amended in the specification, then the substitute specification filed must be accompanied by a statement that it contains no new matter. Such statement must be a verified statement if made by a person not registered to practice before the Office.

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

It is apparent that the 21-6 antibody / hybridoma is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line / hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

It is noted that the sequence of an entire immunoglobulin satisfies the biological deposit of said immunoglobulin. Note that satisfaction for the biological deposit of the specific 21-6 antibody requires the disclosure and recitation of its entire amino acid sequence and not based upon partial sequences.

Given the disclosure and the claims encompassing the instant humanized 21-6 antibody in this application as well as U.S. Patent No. 5,840,299 (IDS, #3); the conditions for the deposit of biological materials under 35 USC 112, first paragraph, with respect to claims 17-26 have been satisfied.

10. Claim 17 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is indefinite in the recitation of "21-6" because its characteristics are not known. The use of "21-6" monoclonal antibody as the sole means of identifying the claimed antibody renders the claim indefinite because "21-6" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct hybridomas or cell lines .

Amending the claims to recite the appropriate ATCC Accession Number would obviate this rejection.

The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined *under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e))*.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claim 1 is rejected under 35 U.S.C. § 102(e) as being anticipated by Wayner et al. (U.S. Patent No. 5,730,978) (see entire document, including Summary of the Invention, Detailed Description of the Invention and Claims). Wayner et al. teach treating methods of suppressing the immune responses to various diseases including rheumatoid arthritis (columns 15-16, Utility of the Invention) with $\alpha 4\beta 1$-specific monoclonal, chimeric and humanized antibodies (columns 11-13, Preparation of Antibodies to Extracellular Matrix Receptors), as well as methods of screening for antagonists (e.g. columns 13-17).
Applicant is reminded that no more of the reference is required than that it sets forth the substance of the claimed invention. The claimed functional limitations would be inherent properties of the referenced methods to treat rheumatoid arthritis with $\alpha 4\beta 1$-specific antibodies.

14. Claims 1 and 17-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wayner et al. (U.S. Patent No. 5,730,978) in view of Bendig et al. (WO 95/19790;IDS, #10).

Wayner et al. teach treating methods of suppressing the immune responses to various diseases including rheumatoid arthritis (columns 15-16, Utility of the Invention) with $\alpha 4\beta 1$-specific monoclonal, chimeric and humanized antibodies (columns 11-13, Preparation of Antibodies to Extracellular Matrix Receptors), as well as methods of screening for antagonists (e.g. columns 13-17).

Wayner et al. differs from the claimed invention by not disclosing the particular 21-6 antibody and humanized 21-26 antibody employed in the claimed methods.

Bendig et al. teach the particular 21-6, including the particular humanized 21-6 antibody employed in the claimed methods (See entire document). Although Bendig et al. does not disclose treating arthritis per se, it does teach the use of the 21-6 antibody to block $\alpha 4$-dependent interactions of VLA-4 in order to block adhesion and to prevent inflammation (see Background of the Invention and the Summary of the Invention on pages 1-5; Testing Humanized Antibodies on page 22; Methods of Treatment on pages 24-26). While Bendig et al. Was more directed towards treating multiple sclerosis, it does teach relying upon testing in EAE models, which were known as models for treating arthritis in addition to multiple sclerosis by the ordinary artisan at the time the invention was made.

Given the ability of the 21-6 antibody to inhibit α4-dependent interactions of VLA-4 to reduce inflammation and its ability to inhibit multiple sclerosis, as taught by Bendig et al., one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the 21-6 antibody, including the humanized 21-6 antibody into other methods of reducing inflammatory conditions, including rheumatoid arthritis, as taught by Wayner et al. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 1 and 17-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wayner et al. (U.S. Patent No. 5,730,978) in view of Monshizadegan et al. (Agents Actions 39: C177-179, 1993; IDS, #25) OR Yednock et al. (U.S. Patent No. 6,033,665) and
further in view of known methods to humanized antibodies of interest for human therapy as taught by Queen et al. (U.S. Patent No. 5,530,101;
IDS, #2), Bendig et al. (WO 92/15683) and Kettleborough et al. (Protein Engineering 4: 773-783, 1991; IDS, #23).

Wayner et al. teach treating methods of suppressing the immune responses to various diseases including rheumatoid arthritis (columns 15-16, Utility of the Invention) with α4β1-specific monoclonal, chimeric and humanized antibodies (columns 11-13, Preparation of Antibodies to Extracellular Matrix Receptors), as well as methods of screening for antagonists (e.g. columns 13-17).

Wayner et al. differs from the claimed invention by not disclosing the particular 21-6 antibody and humanized 21-26 antibody employed in the claimed methods.

Monshizadegan et al. teach the 21-6 VLA-4-specific antibody and its ability to inhibit α4 integrin function of the instant invention (see entire document). It is noted that this was presented at the Sixth International Conference of The Inflammation Research Association. This reference differs from the instant claims by not teaching the humanization of the 21-6 monoclonal antibody.

Yednock et al. teaches the use of α4β1-specific antibodies, including the 21.6 antibody (Example 3 on columns 21-24) to inhibit α4-dependent interactions of VLA-4 to reduce inflammation (see entire document). While Yednock et al. was more directed towards treating inflammatory conditions in the brain, it does teach relying upon testing in EAE models (see Detailed Description of the Invention), which were known as models for treating arthritis in addition to multiple sclerosis by the ordinary artisan at the time the invention was made.

Queen et al. (U.S. Patent No. 5,530,101), Bendig et al. (WO 92/15683) and Kettleborough et al. (Protein Engineering 1991) all teach known methods and the advantages of humanizing antibodies of interest at the time the invention was made (see entire documents).

Although the Monshizadegan et al. and Yednock references are silent about the exact sequences of the 21-6--specific antibodies and the humanized antibodies thereof, the recombinant techniques and computer analyses of CDR grafting as taught by the Queen et al., Kettleborough et al. and Bendig et al. references would have resulted in the same or very nearly the same structural and functional characteristics of the instant claims, since both the references and instant invention use the same techniques, the same antibody specificities and the same goals. The claimed functional limitations encompassed by the claims would be expected properties of selecting for humanized 21-6-specific antibodies to specifically bind and inhibit VLA-4- / α4-specific interactions, including inhibiting adhesion and inflammatory responses, as taught by Wayner et al., Yednock et al. and Monshizadegan et al. The claims drawn to specifically defined humanized antibodies which are obvious, since the record does not contain any evidence that the specifically claimed humanized 21-6 antibodies differ in any significant manner or aspect from that one of ordinary skill in the art would expect to generate using the 21-6 hybridoma as the source of the starting 21-6 antibody in the basic method of generating antibodies and humanizing said antibodies. There appears no evidence that the use of various sources of framework amino acids would differ in an unexpected or distinct manner from those available to the ordinary artisan at the time the invention was made.

Given the ability of the 21-6 antibody to inhibit α4-dependent interactions of VLA-4 to reduce inflammation and its ability to inhibit multiple sclerosis, as taught by Monshizadegan et al. and Yednock, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute the 21-6 antibody, including the humanized 21-6 antibody into other methods of reducing inflammatory conditions, including rheumatoid arthritis, as taught by Wayner et al. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
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